Centers for Education & Research on Therapeutics

a program of the Agency for Healthcare Research and Quality

July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Premarketing Risk Assessment; Docket No. 2004D-0187.

The Centers for Education & Research on Therapeutics (CERTs) appreciate the opportunity to comment on the draft Guidance. The CERTs demonstration program is a national initiative to conduct research and provide education that advances the optimal use of drugs, medical devices, and biological products. The program, authorized by Congress as part of the FDAMA 1997, is administered and funded as a cooperative agreement by the Agency for Healthcare Research & Quality (AHRQ), in consultation with the Food and Drug Administration (FDA). Seven centers (each with a particular population focus), a Coordinating Center, a Steering Committee, and numerous partnerships with public and private organizations make up the CERTs program. Over 200 research and education projects are included in the CERTs portfolio.

Risk management is a critical topic to advance the optimal use of therapeutics. One CERTs initiative aimed at addressing risk management was the organization of a series of "think tank" workshops to identify priority research issues that could improve the nation's ability to assess, communicate, and manage therapeutic risk called the Risk Series. The priority research issues resulting from the Risk Series were announced in March 2003 (see http://www.certs.hhs.gov/programs/risk_series/index.html).

The Guidance addresses several of the issues raised at both the Risk Assessment and Benefit Assessment think-tanks held by CERTs. In particular, the Guidance highlights several important points related to risk assessment of drugs and biologics:

- The Guidance explicitly states that efforts to ensure quality and completeness of a safety database should be comparable to those to support efficacy. To that end, they discuss the use of long term, *controlled* safety studies.

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- In a move to increase the diversity of the pre-approval population of patients, the Guidance recommends to the extent feasible, that only patients with obvious contraindications be excluded from Phase III trials.

- To better characterize the relationship between product exposure and resulting clinical benefit and risk, the Guidance recommends that more than one dose level should usually be used in Phase III trials. It also suggests analyzing adverse events by cumulative dose administered.

- The Guidance suggests use in appropriate circumstances of large simple safety studies (LSSS).

- There is an excellent discussion about analyzing temporal factors when looking at aggregate safety data. The Guidance encourages descriptions of risk as a function of subjects' duration of exposure or as a function of time since initial exposure. It suggests the possibility of generating a hazard rate curve to illustrate changes in risk over time.

In addition, Section V.B addresses the importance of conducting medication error prevention analysis (MEPA) during premarketing risk assessment. The justification and purpose of this step is clearly stated in the Guidance. The Guidance lists several techniques that may be used for MEPA, including Failure Mode and Effects Analysis (FMEA), expert panels, etc., and adds, ***"sponsors should use multiple techniques when performing MEPA assessments."*** (line 496-7) The rationale for this statement is not clear, and may lack an evidence base. The critical point is that whatever technique is used must be comprehensive and systems based. A single technique, if properly selected and applied, may answer all of the relevant questions, while multiple techniques, if not appropriate to the task and not applied properly, may fail to provide adequate information. We recommend a change in wording such as ***"sponsors should use one or more techniques that are comprehensive, systems-based, and appropriate for the range of medication errors that are likely to occur for the product."***

We also suggested drug-disease interactions be included in the list of potential serious adverse effects that should be addressed as a part of all new small molecule drug development programs. (lines 521-29)

In summary, we think the Guidance is excellent, and applaud the FDA for putting forth a thoughtful approach to premarketing risk assessment.

Sincerely,

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